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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,209	HAHN, SOONKAP	
	Examiner	Art Unit	
	KARLHEINZ R. SKOWRONEK	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-16,22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14* is/are allowed.

6)☒ Claim(s) *1,3,5-13,16,22,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1, 3, 5-16, 22, and 24 are pending.

Claims 2, 4, 7-21, 23, and 25 are cancelled.

Claims 1, 3, 5-16, 22, and 24 have been examined.

Claims 1, 3, 5-13, 25, 16, 22, and 24 are rejected.

Clam 14 is allowable.

Claim Objections

Claim 15 is objected to because of the following informalities: claim 15 is missing the article "a" before the term "smaller" (lines 38 and 41) and "larger" (line 41). Appropriate correction is required.

Claim Rejections - 35 USC § 112

Response to Arguments

Applicant's arguments, see remarks p. 13, filed 20 August 2008, with respect to claims 14 and 25 as indefinite under 35 USC 112, second paragraph have been fully considered and are persuasive. The rejection of claims 14 and 25 has been withdrawn in view of the amendments to the claims.

Applicant's arguments filed 20 August 2008 have been fully considered but they are not persuasive. Applicant argues that the amendment to the claim overcomes the rejection of claims 1, 3, 5-13, 15, and 22 as indefinite under 35 USC 112, second paragraph. After consideration of the amended claims, the claims remain indefinite.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,3, 5,-13, 15-16, 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 15 are unclear with respect to step (e). The metes and bounds of step (e) in claims 1 and 15 are indefinite because it is unclear whether "it" is intended to refer to the solid phase or to the single stranded sense product in the phrases "before it hybridizes" and "after it has hybridized thereto". Claims 3, 5-13 and 16 are also rejected because they depend from claims 1 and 15, and thus contain the above issues due to said dependence.

Claim 15 is unclear with respect to the variable K in lines 37-38. The metes and bounds of claim 15 are made indefinite respect to the variable K because it is unclear relative to what the control sample with K repeats is smaller than (i.e. smaller number of repeats than WHAT?).

Claim 15 is unclear in line 37-43. The metes and bounds of claim 15 are made indefinite in line 37-43 because it is unclear which of the two control samples the term "the control sample" refers to.

Claim 15 is unclear in line 39-40. The metes and bounds of claim 15 are made indefinite in lines 39-40 because the claim does not specify what the ratio is that B represents.

Claim 22 is unclear with respect to the term "such" in line 20. The metes and bounds of claim 22 are made indefinite at line 20 because it which hybridization is referred to by the term "such" in line 20; the colorimetric oligonucleotides or the anchoring moieties. Claim 24 is also rejected because it depends from claim 22, and thus contains the above issues due to said dependence.

Claim Rejections - 35 USC § 103

Response to arguments

Applicant's arguments, see Remarks p. 13, filed 18 February 2008, with respect to the rejection of claims 1, 3, 5-14, 22, and 24 as being unpatentable over Kim in view of Beattie et al., in view of O'Connell et al., and in view of Smith et al. under 35 USC 103(a) have been fully considered and are persuasive. The rejection of claims 1, 3, 5-14, 22, and 24 has been withdrawn in view of amendments to the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This rejection is necessitated by amendment of the claims.

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (Korean IPO Pub. No. 10-2000-0072201 Pub Date 17 August 2000), in view of Beattie et al. (US PAT 6,268,147) in view of O'Connell et al. (Clinical genetics, Vol. 61, p. 13-20, 2002), in view of Smith et al. (US PAT 5,753,439), in view of Pollack et al. (Nature Genetics, Vol. 23, p. 41-46, 1999) and Krantz (Dictionary of Algebra, Arithmetic and Trigonometry, CRC Press, Entry "Line", 2001).

The claims are drawn to a method of detecting mutations that are indicative of Fragile X syndrome by testing obtained genomic DNA using labeled oligonucleotides to determine the number of CGG repeats in the obtained genomic DNA.

Kim teaches a method of diagnosing Fragile-X syndrome by using DNA Probes to identify the number of CGG repeats in the obtained genomic DNA. Specifically, Kim teaches obtaining a genomic DNA sample (para. 16). Kim teaches the generation of single stranded DNA (para. 18, line 6). Kim teaches the hybridization of two differentially labeled probes to targets within the denatured each probe directed to a different genomic region of FMR1 gene; one probe being targeted to Short Tandem Repeats (STR) or Short Tandem Repeat Polymorphisms (STRP) CGG or GCC and one probe being targeted to a region of FMR1 gene (para. 48, line 6). Kim shows the immobilization of the labeled target to a solid support (para.18, line 6), separating the hybridized DNA from non-hybridized nucleic acids. Kim teaches measuring the colorimetric intensities of the CY3 and CY5 fluorescent dyes that label the different probes and determining a ratio between cy3 and cy5 then compared to a known control to determine the number of CGG or GCC STR repeats (para. 49). Kim shows that the

target oligonucleotides for the CGG repeats contain 3-10 repeats and specifically show target oligonucleotides for the CGG repeats having 6 triplets (para 49).

Although Kim does not employ PCR directly in the method of identifying the number of STR's in FMR1, Kim shows that the application of PCR to amplify DNA fragments of the region of the FMR1 gene surrounding the CGG STR's can also employed in the analysis of Fragile-X syndrome. The primers of Kim can be used to amplify the same region of FMR1 as the primers of the instant invention. SEQ ID NO:1 of the instant application is targeted to the 5' untranslated region of the FMR1 on the X chromosome. The primer of Kim on paragraph 48, line 6 is directed a similar region of the X chromosome in the 5' untranslated region of FMR and is labeled with biotin. SEQ ID NO: 2 is within the FMR1 gene, 3' to the repeat region. Similarly, Kim shows a primer on paragraph 48, line 5, which targets bases 250-221. The primers of Kim are suitable for PCR amplify the repeat region of the FMR1 5'-untranslated region. Kim shows that the intensities of the 5' untranslated (test) region is compared to the reference region within the FMR1 gene that is 3' to the untranslated region to determine the copy number of CGG repeats in the 5' untranslated region (para. 52). Kim suggests that a method better than electrophoresis and southern blotting is needed to analyze the DNA of the 5' untranslated region FMR1 gene quickly and efficiently.

Kim does not show the use of microarray technology to capture the differentially labeled hybridized target STR's; does not show amplification of DNA by PCR and does not show the use of an exonuclease to generate single stranded DNA.

O'Connell et al. shows the detection of fragile X through a quantitative measurement program for trinucleotide repeats. O'Connell et al. shows the use of PCR to amplify the 5'-untranslated region of FMR1 using oligonucleotides directed to a contiguous region of the FMR1 gene and to a region of the X-chromosome 5' to the repeat region (p.14, col. 1). The primers of O'Connell et al. overlap the primers of SEQ ID NO: 1 and 2. O'Connell shows the primers are used to amplify the 5'-untranslated region of FMR1 containing CGG repeats. O'Connell et al. shows that fragile X testing is usually conducted using PCR. O'Connell et al. shows a method of an optimized PCR amplification method to measure correctly the number of CGG repeats in genomic DNA (p. 14 col. 2 to p. 15 col. 1).O'Connell shows in figure 1 that normal individuals have about 30 repeats and pre-mutation individuals have greater than 60 repeats (figure 1; and p. 13, col. 1-2). It is desirable to measure correctly the number of repeats in the 5'untranslated region of the FMR1 gene because the number of CGG repeats is directly linked to the fragile X phenotype, severity and its diagnosis (p. 13, col. 1-2). O'Connell et al. shows that accurate (CGG)n size determinations are essential to accurate diagnosis of fragile X (p.14, col. 1).

Beattie et al. shows a method of analyzing STRP's by microarray. Beattie et al. shows the use of exonucleases to generate single stranded DNA (col. 29, line 34-43). Beattie et al. shows the advantage to generating single stranded DNA is that re-annealing of complementary target strands can be avoided (col. 29, line 30-32). This is advantageous because the complementary strands may compete with the hybridization of the target strands to the arrayed capture probes (col. 29, line 32-33). Beattie et al.

teach the use of microarray technology to capture nucleic acids (abstract and col. 37-38). Beattie et al. shows that the array has a plurality of spots in which probes to the contiguous segment are linked to a solid support (col. 37).

Smith et al. shows a method of nucleic acid analysis for rapidly determining the length and sequence of a target. Smith et al. shows an array can be constructed to target separately a contiguous sequence and the repeat regions (col. 8, line 41-43). Smith et al. shows that hybridization can be used to rapidly and accurately detect and identify numbers of repeated sequences (col. 4, line 3-6).

Pollack shows a method of determining changes in DNA copy number using comparative genomic hybridization arrays. Pollack et al. shows that fluorescence intensity is detected using the fluorophores, cy3 and cy5 (p.41, col.2-p. 42, col. 1). Pollack et al. shows that the fluorescence intensity ratios provide a representation of copy number variation (p. 41, col. 1). Pollack et al. shows that the fluorescence ratio is determined as the test fluorescence intensity divided by control or reference fluorescence (table 1, legend). Pollack et al. shows that fluorescence ratio increases as DNA copy number increases and the relationship between fluorescence ratio and copy number is linear (figure 2b and 2c; p. 43, col. 1). Pollack et al. show that the method will allow the mapping and identification of genes whose copy number is altered (p.45, col. 2).

Krantz shows that a line can be described as a linear equation. Krantz shows the linear equation can be expressed as real valued function as $f(x) = ax + b$.

It would have been obvious to one of skill in the art to modify the method of Kim differentially targeting the CGG repeats and a 3'- contiguous region using different colorimetric probes with the method of amplifying the 5'-untranslated region of FMR1 containing CGG repeats of O'Connell and the method of producing single stranded DNA using the exonuclease of Beattie and the plurality of targeting probes of Smith et al, because O'Connell et al. shows that accurate CGG size determinations are essential to accurate diagnosis of fragile X. It would have been further obvious to modify Kim with O'Connell et al., Beattie et al., and Smith et al. because Beattie et al. shows the advantage to generating single stranded DNA is that re-annealing of complementary target strands can be avoided because the complementary strands may compete with the hybridization of the target strands to the arrayed capture probes. It would have been obvious to one of ordinary skill in the art to modify the method of detecting copy number of Kim et al. in view of O'Connell et al., in view of Smith et al. and in view of Beattie et al. with the enumeration of copy number of Pollack as linear real valued function of Krantz because all the claimed elements were known, in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention. The claimed equation $N = K + \frac{(A-B)Q}{(C-B)}$ is a form of a real valued function. In the claimed equation the variable, K, is the intercept and corresponds to the variable, b, of the real valued function. The slope, a, of the real valued function is represented in

the claimed function as $\frac{Q}{(C-B)}$ and shown graphically in figure 2b and 2c of Pollack et al. As defined by the claim, Q is the difference in copy number divided by the difference in the fluorescence ratios of two known copy number states. The variables A, B, and C are fluorescence ratios representing the fluorescence intensity of the 5' untranslated CGG repeated (test) region divided by the fluorescence intensity of the (reference) region within the FMR1 gene that is 3' to the untranslated region, similar to the fluorescence ratios of Pollack et al. Thus based on the elements that were known in the art at the time of invention, one of ordinary skill in the art had it with their capabilities to express the linear relationship between fluorescence ratio and copy number as real valued function in order to determine the number of copies in a an unknown sample determine the copy number of the sample. It would have been further obvious to modify Kim with O'Connell et al., Beattie et al., and Smith et al. because Smith et al. shows that hybridization can be used to rapidly and accurately detect and identify numbers of repeated sequences.

Response to arguments

Applicant's arguments filed 20 August 2008 have been fully considered but they are not persuasive. The argument is that amendment of the claims to recite a general form of the enumeration function in not shown by Kim with O'Connell et al., Beattie et al., and Smith et al. The argument is not persuasive because Kim with O'Connell et al., Beattie et al., Smith et al., Pollack et al. and Krantz suggests the generic form of the function.

Allowable Subject Matter

Claim 14 is allowable because the prior art does not show or suggest the function $N = 30 + (A - 1.03)66.4$.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571) 272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. R. S./
Examiner, Art Unit 1631

30 November 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631